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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,763	06/05/2006	Vincenzo De Leo	SER-105	2323

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EXAMINER	
BORGEEST, CHRISTINA M	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,763	DE LEO ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *24 January 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of the species of spermatozoa diploidy in the reply filed on 23 June 2008, reading on claims 12, 13, 14, 16-21 and 26-29, is acknowledged. However, upon further consideration this species election is hereby withdrawn. Claims 12-29 are under examination.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite a method for the reduction and/or treatment of gamete chromosomal abnormalities in a male (or alternatively, treatment of aneuploidy, diploidy and disomy in a male) comprising the administration of a pharmaceutically active amount of FSH or FSH variant to the male in need thereof, however, the claims do not contain an active method step stating what the effect is supposed to be. The rejection could be overcome with an inclusion of the active step such as: wherein the effective amount is sufficient to reduce or treat the rate of aneuploidy, diploidy and/or disomy in a male patient), as stated at paragraph [0050] of the instant specification.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The main issues leading to the rejection of enablement concern the breadth of the claims, the nature of the invention, the existence of working examples, the state of the prior art and the level of predictability in the art. The state of the prior art indicates

FSH treatment in males with hypogonadotrophic hypogonadism and certain types of infertility (discussed below). Although Applicants provide working examples of a reduction in diploidy and aneuploidy in human patients (see Examples 1-4 of the instant specification), the examples are flawed in that there are no controls. Secondly, the art teaches of the unpredictability of treatment of sperm aneuploidy, diploidy and disomy with FSH, and the negative reports in the art must be given some consideration by the Examiner. In short, the preponderance of evidence in the art suggests that chromosomal abnormalities in sperm cannot be treated with FSH. Another complicating factor is that the art also teaches that elevated FSH levels in males is correlated with high levels of sperm chromosomal abnormalities, thus this does not suggest to one of skill in the art that treatment of these disorders can be achieved by administering more of the very substance to patients that they have too much of. It is noted that the participants in the instant study had normal hormone levels, including normal FSH levels. Thus even if the working examples were sufficient, the claims are not commensurate in scope with the evidence presented in the specification because the claims are not limited to treatment of males with normal FSH levels. Finally, with regard to claims 12, 16-21 and 26-28, the preamble specifies reduction and treatment of "gamete chromosomal alterations", which is much broader in scope than what was studied in the specification, specifically, sperm aneuploidy, sperm diploidy or sperm disomy. For example, gamete chromosomal alterations read on broken or fragile chromosomes, genes encoding genetic disorders, etc.Thus again, even if the working

examples were sufficient, the claims are not commensurate in scope with the evidence presented in the specification.

Regarding FSH levels and genetic defects, according to Faure et al. (International Journal of Andrology; 2007: 30: 153-162), elevated FSH levels are significantly correlated with higher risk of high sperm disomy (abnormal chromosome represented twice) rates, meiotic abnormalities (see p. 160, entire left column), as well as sperm aneuploidy (see p. 158, right column, last paragraph). Levron et al. (MCE, 2001; 183: S23-S28) teach that elevated serum FSH levels correlated with aneuploidy and disomy (see p. 25, Table 1) and they go on to say, "[e]levated serum FSH level is the hallmark of gonadal insufficiency and reproductive senescence in both males and females." Barri et al. (RBM Online, 2005; 10: 735-739) teach that patients with higher than normal serum FSH levels had significantly more meiotic abnormalities, and that "[a]fter multivariate analysis, sperm concentration and serum FSH concentration were the only independent predictive factors of abnormal meiotic pattern," (see p. 736, left column, penultimate paragraph), in other words, high FSH levels were predictive of chromosomal abnormalities. This suggests to one of skill in the art that treatment of males with genetic or chromosomal abnormalities in sperm with FSH would not be indicated since this population of males have high levels of serum/plasma FSH.

Regarding the intersection between elevated FSH levels and treatment of male infertility, Dr. Carlo Foresta (RBM Online, 2007; 15: 666-72) reported that men with high plasma FSH concentrations did not respond to FSH treatment (see Table 2, p. 669 and p. 671, left column, 1st full paragraph). The failure of FSH to treat infertile men with

elevated FSH levels occurred ***regardless of the reason for the infertility, i.e., with or without genetic or chromosomal abnormalities, FSH treatment failed when the patients had elevated serum FSH***. Again, although the working examples teach that the treatment of infertile males with normal FSH levels, the claims encompass treatment of males with elevated FSH levels. Regarding treatment with FSH in males with chromosomal or genetic abnormalities in sperm, according to a review article by Baccetti et al. (Contraception, 2002; 65: 283-287), that ***abnormalities correlated to genetic mutations are unaffected by FSH treatment*** (see p. 284, right column, penultimate paragraph). Baccetti et al. (Human Reprod. 1997; 12: 1955-1968—reference R2 submitted on Applicants' 1449 form) explicitly teach that as a result of their analysis of the efficacy of FSH treatment for patients with different types sperm defects that those "with genetic defects...should not be treated with FSH" (see p. 1967, left column, last paragraph). Finally, according to Foresta (cited above), in "the presence of hypospermatogenesis associated with post-meiotic alterations, ***FSH further amplified the maturation difficulties in the final phases of spermatogenesis***..." (see p. 667, right column, 1st full paragraph). In summary, these articles suggest to one of skill in the art that 1) FSH treatment for infertility is not effective in males with elevated levels of FSH and 2) FSH treatment for infertility is not effective in males with sperm genetic or chromosomal abnormalities.

Finally, by way of explanation of terms in the art, note that "oligozoospermic men" have "elevated levels of XY aneuploidy and diploidy in the germ-line, as well as elevated levels of sperm chromatin disturbances and sperm DNA strand breaks. These

data demonstrate that oligozoospermic infertility patients show several different types of genetic damage in their sperm." (See abstract, whole document of Schmid et al., Human Reproduction, 2003; 18: 1474-1480). In other words, oligospermic men have abnormal chromosomal alterations in their sperm. In summary, the prior art teaches that treatment of men with gamete chromosomal alterations with FSH has equivocal results, thus underscoring the state and unpredictability of the prior art.

Due to the complex nature of the invention, i.e., treatment of male infertility, the state and the unpredictability of the prior art, which teaches that gamete chromosomal abnormalities are not treatable with FSH, the working examples, which do not include controls, and finally, the breadth of the claims, which are not commensurate in scope with the working examples in the specification or the literature (i.e., "gamete chromosomal abnormalities" is broad and the working examples only teach treatment of aneuploidy/diploidy/disomy; the claims encompass FSH treatment of males with elevated FSH levels, whereas working examples and literature teach this is untenable), undue experimentation would be required of the skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12-27 and 29 are rejected under 35 U.S.C. 102(b) as being anticpated by Foresta et al. (Fertil Steril. 2002, 77: 238-244—hereafter "Foresta 2002").

Note that the preamble of the claims, "reduction and/or treatment of gamete chromosomal alterations in a male" is not given patentable weight, since there is no active method step that specifies that the effective amount is sufficient to reduce or treat the rate of aneuploidy, diploidy and/or disomy in a male patient (see Rejection under 112, second paragraph). Therefore, the claims encompass administration of FSH to males in need of treatment with FSH, for example, males with hypogonadotrophic hypogonadism, or some other art recognized ailment that is treatable with FSH.

Foresta (2002) et al. teach that rFSH is a safe and effective treatment in human males with moderate hypospermatogenesis and normal FSH levels (see p. 244, left column, last paragraph) at a dose of 100 IU on alternate days (see p. 243, right column, 2nd paragraph), thus meeting the claim limitations of claims 12-27 and 29, because the phrase "at or about 150 IU/dose" is given its broadest reasonable interpretation, and 100 IU is "at or about 150 IU/dose." Foresta (2002) is silent with respect to the patients having chromosomal abnormalities such as sperm diploidy, disomy or aneuploidy. Nevertheless, Foresta (2002) teach administration of the same substance (rFSH) to the same patient population (infertile males). Furthermore, as stated in the rejection under 35 U.S.C. 112, second paragraph, the claims do not contain an active method step stating that the effective amount is sufficient to reduce or treat the rate of aneuploidy,

including diploidy and/or disomy in a male patient, thus the claims are interpreted as administration of FSH to infertile males for any reason.

Claims 12-17, 19-27 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Acosta et al. (Fertil Steril. 1991; 55: 1150-6). Note that the preamble of the claims, "reduction and/or treatment of gamete chromosomal alterations in a male" is not given patentable weight, since there is no active method step that specifies that the effective amount is sufficient to reduce or treat the rate of aneuploidy, diploidy and/or disomy in a male patient (see Rejection under 112, second paragraph). Therefore, the claims encompass administration of FSH to males with hypogonadotrophic hypogonadism, or some other art recognized ailment that is treatable with FSH.

Acosta et al. teach treatment of infertile males with pure FSH at a dose of 150 IU three times a week for 3 months with the result that six healthy, full-term pregnancies were achieved (see abstract; p. 1151, right column, last full paragraph; p. 1154, right column, penultimate paragraph; p. 1155, right column, 4th paragraph). Acosta et al. meet the exact limitations of the dose of FSH (between 75-300 IU/dose or 150 IU/dose) and frequency of administration (i.e., three times a week or every other day). Note that in this rejection, "at or about 150 IU/dose" is interpreted more narrowly. Acosta et al. are silent with respect to the patients having chromosomal abnormalities such as sperm diploidy, disomy or aneuploidy. Nevertheless, Acosta et al. teach administration of the same substance (FSH) to the same patient population (infertile males). Furthermore, as stated in the rejection under 35 U.S.C. 112, second paragraph, the claims do not

contain an active method step stating that the effective amount is sufficient to reduce or treat the rate of aneuploidy, including diploidy and disomy in a male patient, thus the claims are interpreted as administration of FSH to infertile males for any reason.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Acosta et al. (cited above) as applied to claims 12-17, 19-27 and 29 above and further in view of Bouloux et al. (Human Reprod. 2001, 16: 1592-1597).

Note that the preamble of the claims, "reduction and/or treatment of gamete chromosomal alterations in a male" is not given patentable weight, since there is no active method step that specifies that the effective amount is sufficient to reduce or treat

the rate of aneuploidy, diploidy and/or disomy in a male patient (see Rejection under 112, second paragraph). Therefore, the claims encompass administration of FSH to males with hypogonadotrophic hypogonadism, or some other art recognized ailment that is treatable with FSH.

The first issue that must be examined when considering obviousness is to determine the scope and contents of the prior art. The discussion in the preceding rejection of how Acosta et al. meet the limitations of the claims is applicable here and is hereby incorporated. The second issue is to ascertain the differences between the prior art and the claims at issue. Acosta et al. do not teach the administration of CTP-FSH, which is a variant of FSH. Bouloux et al. teach that FSH is safe and effective because it could lead to more convenient dosing regimens (i.e., the longer half life decreases the need for frequent injections—see p. 1592, right column, and p. 1596, right column, last paragraph). Given this teaching, it would be obvious to one of ordinary skill in the prior art (the POSITA) to substitute CTP-FSH for FSH because the level of skill in the art concerning knowledge of FSH variants and determining dosing regimens for variants is high, and given the evidence presented in Bouloux et al. that the FSH-CTP was well tolerated, the POSITA could expect to substitute one FSH variant for another with a reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 8:00am - 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646